Intrathecal immunoglobulin production in patients with systemic lupus erythematosus with neuropsychiatric manifestations

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Neuropsychiatric manifestations have been reported in 30–60% of patients with systemic lupus erythematosus (SLE), with variable IgG synthesis in cerebrospinal fluid (CSF).[1] In this study, we sought to examine intrathecal IgG synthesis measured qualitatively as the IgG index,[2] calculated using the formula

(IgG CSF/IgG serum)/(albumin CSF/albumin serum),

and quantitatively as oligoclonal bands (OCBs) by isoelectric focusing (IEF)[3] in patients with SLE with various neurological presentations, and to determine the cut-off of the IgG index for the detection of these pathological IgG.

CSF results were retrieved from a database of 2902 samples using the keywords ''SLE'' or ''lupus''. Only the first CSF sample taken before treatment for each neurological episode in each patient was analysed. Samples from traumatic subarachnoid haemorrhage were excluded. Cases were ascertained according to the American College of Rheumatology classification criteria.[4] Neurological presentations were classified into neuropsychiatric

Abbreviations: CSF, cerebrospinal fluid; IEF, isoelectric focusing; OCB, oligoclonal band; NPSLE, neuropsychiatric SLE; SLE, systemic lupus erythematosus

Table 1 Discrepancy in intrathecal IgG production according to qualitative and quantitative methods and the presence of serum hypo- and hypergammaglobulinaemia in patients with systemic lupus erythematosus with inflammatory and non-inflammatory neurological manifestations

Neuropsychiatric manifestations	(n)	Total	Positivity by IEF (%)	Positivity by IgG index (%)	Discrepancy* (%)	Negative by IEF, positive by IgG index (%)	Serum IgG level (%)			
							I	II	III	I+III
Inflammatory		49	13 (26.5)	32 (65.3)	26 (53.1)	25 (51.0)	5 (10.2)	30 (61.2)	14 (28.6)	19 (38.8)
NPSLE		38	10 (26.3)	25 (65.8)	22 (57.9)	21 (55.3)	3 (7.9)	22 (57.9)	13 (34.2)	16 (42.1)
Aseptic meningitis		2	1 (50)	1 (50)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)
Transverse myelitis		7	1 (14.3)	7 (100)	6 (85.7)	6 (85.7)	0 (0)	4 (57.1)	3 (42.9)	3 (42.9)
Seizure		11	1 (9.1)	7 (63.6)	6 (54.5)	6 (54.5)	2 (18.2)	7 (63.6)	2 (18.2)	4 (36.4)
Peripheral neuropathy		6	2 (33.3)	5 (83.3)	3 (50)	3 (50)	0 (0)	2 (33.3)	4 (66.7)	4 (66.7)
Optic neuritis	2									
VI nerve palsy	2									
L2–5 polyradiculopathy	1									
Mononeuropathy	1									
Cognitive dysfunction, psychosis and acute confusion		12	5 (41.7)	10 (83.3)	7 (58.3)	6 (50)	1 (8.3)	7 (58.3)	4 (33.3)	5 (41.6)
Central nervous system infection		11	3 (27.3)	7 (63.6)	4 (36.4)	4 (36.4)	2 (18.2)	8 (72.7)	1 (9.1)	3 (27.3)
Meningitis										
Bacterial meningitis	1									
Tuberculous meningitis	3									
Cryptococcal meningitis	3									
Encephalitis	4									
Non-inflammatory		13	0 (0)	7 (53.8)	7 (53.8)	7 (53.8)	1 (9.1)	9 (81.8)	3 (27.3)	4 (36.4)
Focal NPSLE		5	0 (0)	4 (80)	4 (80)	4 (80)	0 (0)	2 (40)	3 (60)	3 (60)
Cerebellar infarct	2									
Thalamic infarct	1									
Sagittal sinus thrombosis	1									
Brainstem infarct	1									
Associations		2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)
Thrombotic thrombocytopenic purpura	1									
Steroid-induced psychosis	1									
Other conditions		6	0 (0)	3 (50)	3 (50)	3 (50)	1 (16.7)	5 (83.3)	0 (0)	1 (16.7)
Idiopathic epilepsy	3									
Sepsis	2									
Depression	1									
Unclassifiable condition†		1	—	—	—	—	—	—	—	—

I, Hypergammaglobulinaemia
II, normal gammaglobulin level.
III, Hypergammaglobulinaemia
IEF, isoelectric focusing; n, number of patients with condition; NPSLE, neuropsychiatric systemic lupus erthematosus.
*Discrepancy = positive IEF/negative IgG index and negative IEF/positive IgG index.
†Patient died before further investigations could be arranged. The unclassifiable case was excluded in subsequent analysis of the association between intrathecal IgG production and neurological presentations.

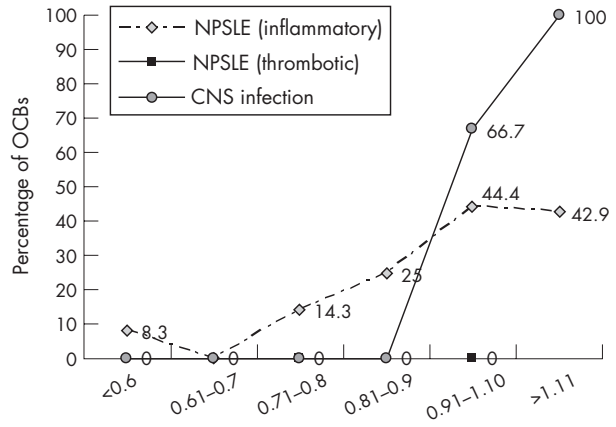

Figure 1 Detection rate of cerebrospinal fluid oligoclonal bands (OCBs) in different ranges of IgG index in inflammatory and non-inflammatory neurological conditions in patients with systemic lupus erythemaosus. CNS, central nervous system; NPSLE, neuropsychiatric systemic lupus erythematosus.

SLE (NPSLE) according to the American College of Rheumatology criteria[5] and other non-NPSLE conditions. A total of 57 results from 54 patients were eligible for the analysis.

The 63 neurological presentations among the 57 neurological episodes were classified as inflammatory (n = 49) and non-inflammatory (n = 13) according to the underlying pathogenesis determined by clinical features, MRI findings and response to immunosuppressive treatment. Table 1 shows the distribution of CSF OCBs, positive IgG index (>0.6) and the discrepancy between the two methods among these conditions. CSF OCBs were more frequently detected in inflammatory (26.5%) than in non-inflammatory conditions, including focal NPSLE and non-SLE-related conditions (0%; p = 0.05), but not for positive IgG index (p = 1.0). The different rates of detection of CSF OCBs in NPSLE reflected heterogeneity in the underlying pathogenesis where microthrombi or vasculitis may cause damage to the blood–brain barrier.[6–8] Although serum autoantibodies that cross react with antigens present in brain tissue have been shown to cause neuronal death through a damaged blood–brain barrier in the mouse model,[9] our study suggested intrathecal synthesis of autoantibodies as another possible pathogenetic mechanism.

There was agreement between IEF and IgG index on the presence (17.5%, n = 10) and absence (31.6%, n = 18) of intrathecal IgG synthesis, giving a discrepancy rate of 50.9% (29/56). This discrepancy was found to correlate with the presence of serum hypogammaglobulinaemia or hypergammaglobulinaemia (r = 0.86, p = 0.004), which was present in 23 (40.3%) samples. This suggested a non-linear relationship between the IgG ratio and the albumin ratio in the formula for IgG in these ranges of IgG.[10] IEF is thus superior to the IgG index for detection in patients with SLE.

CSF OCBs were found to correlate with the IgG index in inflammatory neurological conditions with higher sensitivity using a higher cut-off of the IgG index (≥0.81; fig 1). The presence of CSF OCBs irrespective of the IgG index may suggest a specific immune response, whereas quantitatively increased IgG without OCBs might indicate a non-specific polyclonal response. Studies on the specificities of CSF OCBs may provide clues to the underlying pathogenesis.

In conclusion, our study showed that intrathecal production of IgG was found in inflammatory NPSLE. IEF is the preferred method of detection. Other investigation results should be considered for diagnosis because of its lack of discriminative power for NPSLE and CNS infections.

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REFERENCES

1 **West SG**. Neuropsychiatric lupus. *Rheum Dis Clin North Am* 1994;**20**:129–58.
2 **Link H**, Tibbling G. Principles of albumin and IgG analysis in neurological disorders. The evaluation of IgG synthesis within CNS in multiple sclerosis. *Scand J Clin Lab Invest* 1977;**37**:385–401.
3 **Correale J**. Oligoclonal bands and antibody responses in multiple sclerosis. *J Neurol* 2002;**249**:375–89.
4 **Tan EM**, Cohen AS, Fries JF, Masi A T, McShane D J, Rothfield N F, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271–7.
5 **ACR Ad hoc Committee on Neuropsychiatric Lupus Nomenclature**. The American College of Rheumatology Nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;**42**:599–608.
6 **Kerr DA**, Ayetey H. Immunopathogenesis of acute transverse myelitis. *Curr Opin Neurol* 2002;**15**:339–47.
7 **Lampropoulos CE**, Hughes GR. The antiphospholipid (Hughes') syndrome: changing the face of neurology. *Eur J Intern Med* 2004;**15**:147–50.
8 **Abbott NJ**, Mendonca LL, Dolman DE. The blood-brain barrier in systemic lupus erythematosus. *Lupus* 2003;**12**:908–15.
9 **Kowal C**, DeGiorgio LA, Nakaoka T, Hetherington H, Herta PT, Diamond B, *et al*. Cognition and immunity; antibody impairs memory. *Immunity* 2004;**21**:179–88.
10 **Mclean BN**, Luxton RW, Thompson EJ. A study of immunoglobulin G in the cerebrospinal fluid of 1007 patients with suspected neurological disease using isoelectric focusing and the log IgG-index. *Brain* 1990;**113**:1269–89.

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CORRECTION

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An error occurred in the February 2007 issue of the journal (Iannone F, Trotta F, Monteccuco C, Giacomelli R, Galeazzi M, Matucci-Cerinic M, *et al*. Etanercept maintains the clinical benefit achieved by infliximab in patients with rheumatoid arthritis who discontinued infliximab because of side effects. *Ann Rheum Dis* 2007;66:249–52.) The correct spelling of the third author's name is Montecucco C.